PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTAVALISSE®

Fostamatinib tablets

100 mg, 150 mg fostamatinib (as fostamatinib disodium hexahydrate)

Antihemorrhagics (ATC Code: B02BX09)

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RECENT MAJOR LABEL CHANGES

Not applicable.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TAVALISSE™ (fostamatinib disodium hexahydrate) is indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to other treatments.

TAVALISSE treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of hematological diseases.

1.1 Pediatrics

Pediatrics (<18 years of age): TAVALISSE is not indicated for use in patients less than 18 years of age and young adults until growth is complete. [see *WARNINGS AND PRECAUTIONS, Bone Remodelling* and *Special Populations, Pediatrics*].

1.2 Geriatrics

Geriatrics (≥65 years of age): The incidence of adverse events was higher in the geriatric population. No overall differences in effectiveness were observed in these patients compared to younger patients. [see *WARNINGS AND PRECAUTIONS, Geriatrics]*

2 CONTRAINDICATIONS

TAVALISSE is contraindicated:

- in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see *DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING*.
- during pregnancy *[See WARNINGS AND PRECAUTIONS, Sexual Health and Special Populations]*

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The following factors should be considered when dosing TAVALISSE:

- TAVALISSE dosing requirements must be individualised based on the patient's platelet counts and tolerability. [see *Recommended Dose and Dosage Adjustment*].

Drug Interactions

- Concomitant use with strong CYP3A4 inhibitors increases exposure to R406. Monitor for toxicities that may require TAVALISSE dose modifications when given with a strong CYP3A4 inhibitor. TAVALISSE should not be used with strong CYP3A4 inducers *[see Recommended Dose and Dosage Adjustment and DRUG INTERACTIONS].*

4.2 Recommended Dose and Dosage Adjustment

Initiate TAVALISSE at a dose of 100 mg taken orally twice daily. After 4 weeks, if platelet count has not increased to at least 50×10^9/L, increase TAVALISSE dose to 150 mg twice daily.

Use the lowest dose of TAVALISSE to achieve and maintain a platelet count of at least 50×10^9 /L as necessary to reduce the risk of bleeding.

A daily dose of 300 mg must not be exceeded.

Efficacy has not been established at lower doses recommended for the management of adverse reactions.

Discontinuation

Discontinue TAVALISSE after 12 weeks of treatment if the platelet count does not increase to at least 50 $\times 10^9$/L.

Dose interruption, reduction, or discontinuation may be required to manage adverse reactions including diarrhea, hypertension, hepatotoxicity, and neutropenia *(*see Table 2*)*.

A dose reduction schedule is provided in Table 1, based on daily dose.

Table 1 Dose Reduction Schedule

Daily Dose	Administered as:	
	AM	PM
300 mg/day	150 mg	150 mg
200 mg/day	100 mg	100 mg
150 mg/day	150 mg[1]	---
100 mg/day[2]	100 mg[1]	---

[1] Once daily TAVALISSE should be taken in the morning.
[2] If further dose reduction below 100 mg/day is required, discontinue TAVALISSE.

The recommended dose modifications for adverse reactions are provided in Table 2.

Table 2 Recommended Dose Modifications and Management for Specific Adverse Reactions

Adverse Reaction	Recommended Action
Hypertension	
Stage 1: systolic 130-139 or diastolic 80-89 mmHg	Initiate or increase dosage of antihypertensive medication and adjust until blood pressure (BP) is controlled. If the BP target is not met, reduce TAVALISSE to next lower daily dose (See Table 1).
Stage 2: BP ≥140-159 mmHg systolic and/or ≥90-99 mmHg diastolic	Initiate or increase dosage of antihypertensive medication, and adjust until BP is controlled. If BP remains ≥140 systolic and/or ≥90 mmHg diastolic, reduce TAVALISSE to next lower daily dose (See Table 1).
BP 160-179 mmHg systolic or 100-109 mmHg diastolic	Initiate or increase dosage of antihypertensive medication, and adjust until BP is controlled. If BP remains ≥160-179 systolic or ≥100-109 diastolic, interrupt or discontinue TAVALISSE.

Adverse Reaction	Recommended Action
Hypertensive crisis: BP ≥180 systolic and/or ≥110 mmHg Or symptomatic at any BP level	Interrupt or discontinue TAVALISSE. Initiate or increase dosage of antihypertensive medication, and adjust until BP is controlled. If BP returns to less than the target BP, resume TAVALISSE at same daily dose. If repeat BP is ≥160/100 mmHg despite aggressive antihypertensive treatment, discontinue TAVALISSE.
Hepatotoxicity	
AST or ALT ≥3x to <5 x ULN	If patient is symptomatic (nausea, vomiting, abdominal pain), interrupt TAVALISSE. Recheck LFTs every 72 hours until ALT or AST values are <1.5x ULN and total BL remains <2x ULN. Resume TAVALISSE at next lower daily dose (See Table 1).
	If patient is asymptomatic, recheck LFTs every 72 hours until ALT or AST are <1.5x ULN and total BL remains <2x ULN. Interrupt or reduce dose of TAVALISSE if ALT or AST remains 3 to 5x ULN and total BL remains <2 x ULN. If interrupted, resume TAVALISSE at next lower daily dose (refer to Table 1) when ALT or AST are no longer elevated (<1.5x ULN) and total BL remains <2x ULN.
AST or ALT ≥5 x ULN and total BL <2 x ULN	Interrupt TAVALISSE. Recheck LFTs every 72 hours: If AST and ALT decrease, recheck until ALT and AST are <1.5x ULN and total BL remains <2x ULN; resume TAVALISSE at next lower daily dose (See Table 1). If AST or ALT persist at ≥5x ULN for 2 weeks or more, discontinue TAVALISSE.
AST or ALT ≥3 x ULN and total BL >2 x ULN	Discontinue TAVALISSE.
Elevated unconjugated (indirect) BL in absence of other LFT abnormalities and no signs of liver impairment.	Continue TAVALISSE with frequent monitoring since isolated increase in unconjugated (indirect) BL may be due to UGT1A1 inhibition.
Diarrhea	
Diarrhea	Manage diarrhea using supportive measures (dietary changes, hydration and/or antidiarrheal medication) early after the onset until symptom(s) have resolved. If symptom(s) become severe (Grade 3 or above), interrupt TAVALISSE. If diarrhea improves to mild (Grade 1), resume TAVALISSE at the next lower daily dose (See Table 1).

Adverse Reaction	Recommended Action
Neutropenia	
Neutropenia	If absolute neutrophil count decreases (ANC <1.0 x 10^9/L) and remains low after 72 hours, interrupt TAVALISSE until resolved (ANC >1.5 x 10^9/L). Resume TAVALISSE at the next lower daily dose (refer to Table 1).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BL = bilirubin; ULN = upper limit of normal; LFT = liver function tests (AST, ALT, total BL with fractionation if elevated, alkaline phosphatase); ANC = absolute neutrophil count

Drug Interactions

Concomitant use with strong CYP3A4 inhibitors increases exposure to R406 (the major active metabolite). Monitor for toxicities of TAVALISSE that may require TAVALISSE dose modifications (see Table 1) when given concurrently with a strong CYP3A4 inhibitor *[see* DRUG INTERACTIONS*].*

TAVALISSE should not be used with strong CYP3A4 inducers [*see DRUG INTERACTIONS*].

Renal Impairment: No dose adjustment is necessary in patients with renal impairment.

Hepatic Impairment: TAVALISSE should not be used in patients with severe hepatic impairment. In patients with mild or moderate hepatic impairment, liver function should be monitored throughout therapy with TAVALISSE. Dose regimen adjustment may be required (see Table 1 and Table 2, and *WARNINGS AND PRECAUTIONS*).

Geriatrics (≥65 years of age): No dose adjustment is necessary in older patients [see *WARNINGS AND PRECAUTIONS, Geriatrics*].

Pediatrics (<18 years of age): TAVALISSE is not indicated in patients less than 18 years of age and young adults until growth is complete because of adverse reactions on actively growing bones observed in non-clinical studies [see *WARNINGS AND PRECAUTIONS, Bone Remodelling*].

4.3 Administration

TAVALISSE is for oral use. The tablets should be taken whole with or without food. In the event of gastric upset, tablets may be taken with food.

4.4 Reconstitution

TAVALISSE is supplied as a film-coated tablet, and therefore does not require reconstitution.

4.5 Missed Dose

In the case of a missed dose of TAVALISSE, instruct patients to take their next dose at the regularly scheduled time.

5 OVERDOSAGE

There is no specific antidote for overdose with TAVALISSE, and the amount of R406 (the pharmacologically active metabolite of fostamatinib) cleared by dialysis is negligible. In the event of an overdose, monitor patient closely for signs and symptoms of adverse reactions, and treat the reactions with supportive care [see *WARNINGS AND PRECAUTIONS* and *ADVERSE REACTIONS*].

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	tablet 100 mg 150 mg	• Magnesium stearate • Mannitol • Povidone • Sodium bicarbonate • Sodium starch glycolate • Film coating*
*Contains polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide yellow and iron oxide red		

- TAVALISSE 100 mg tablets: orange, film-coated, round, biconvex tablets debossed with "100" on one side and "R" on the reverse side. Each film-coated tablet contains 100 mg of fostamatinib equivalent to 126.2 mg of fostamatinib disodium hexahydrate.
- TAVALISSE 150 mg tablets: orange, film-coated, oval, biconvex tablets debossed with "150" on one side and "R" on the reverse side. Each film-coated tablet contains 150 mg of fostamatinib equivalent to 189.3 mg of fostamatinib disodium hexahydrate.
- TAVALISSE tablets are available in bottles of 30 or 60 tablets with 2 desiccant canisters.

7 WARNINGS AND PRECAUTIONS

Bone remodelling

Since TAVALISSE was shown *in vitro* to target SYK and other tyrosine kinases that are involved in bone metabolism (VEGFR, RET), any potential untargeted effects on bone remodelling or formation remain undetermined. Based on non-clinical data, the potential risks in actively growing bones include chondrodystrophy and growth plate dysplasia. TAVALISSE is therefore not indicated in children and young adults where epiphyseal fusion has not yet occurred.

Closer monitoring of patients with osteoporosis and patients with fractures is also recommended. The benefit risk of continuing therapy in these patients should be thoroughly evaluated by the Prescriber.

Cardiovascular

Hypertension

Hypertension was reported in 28% of patients (17% mild, 9% moderate, 2% severe,1% serious) treated with TAVALISSE (13% of placebo-treated patients). Hypertensive crisis occurred in 1 patient treated with TAVALISSE. Hypertension resulted in dose reduction or interruption in 4 TAVALISSE-treated patients (no placebo-treated patients) and resulted in discontinuation in 1 patient treated with TAVALISSE.

Patients with pre-existing hypertension are possibly more susceptible to the hypertensive effects of TAVALISSE. Approximately 20% of TAVALISSE-treated patients (17% of placebo-treated patients) required intervention for hypertension-related events, either an increase in antihypertensive medications and/or a new antihypertensive medication. Hypertension was

unresolved in 5% of patients at end of study.

Monitor blood pressure every 2 weeks until stable, then monthly. Adjust or initiate antihypertensive therapy to control blood pressure during TAVALISSE therapy. If increased blood pressure persists, interrupt, reduce or discontinue TAVALISSE [see *DOSAGE AND ADMINISTRATION*, *Recommended Dose and Dosage Adjustment*].

Heart Rate and Conduction Abnormalities

In a dedicated clinical electrocardiographic (ECG) assessment study in healthy subjects, dose-dependent mild heart rate lowering effect and uncorrected PR interval prolongation were observed that were not considered clinically relevant. [see *ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology*].

In the Phase 3 clinical program, no apparent cardiac safety issues were observed when TAVALISSE was administered to patients with low heart rate (less than 60 beats per minute). Due to the limited number of patients studied, the use of TAVALISSE in patients with very low heart rate (less than 50 beats per minute) should be carefully considered to determine whether the therapeutic benefit outweighs the potential risk.

Driving and Operating Machinery

Patients should avoid driving or using machines if feeling dizzy.

Gastrointestinal

Diarrhea occurred in 31% of patients (21% mild, 10% moderate, 1% severe, 1% serious) treated with TAVALISSE (15% of placebo-treated patients). Antidiarrheal medication was administered in 13% of TAVALISSE-treated patients and 10% of placebo-treated patients. Diarrhea events led to dose interruption or reduction in 5% of patients, discontinuation in 1% of patients, and was unresolved in 3% of patients treated with TAVALISSE at the end of the study.

Monitor patients for the development of diarrhea. Manage diarrhea using supportive care measures, including dietary changes, hydration and/or antidiarrheal medication, early after the onset of symptoms. Interrupt, dose reduce, or discontinue TAVALISSE if diarrhea becomes severe (Grade 3 or above). [see *DOSAGE AND ADMINISTRATION*, *Recommended Dose and Dosage Adjustment*].

Nausea was reported in 19% of TAVALISSE-treated patients (8% of placebo-treated patients). Abdominal pain was reported by 7% of TAVALISSE-treated patients (4% of placebo-treated patients).

Hematologic

Neutropenia

Neutropenia occurred in 7% of patients treated with TAVALISSE; febrile neutropenia and severe neutropenia occurred in 1% of patients each, and neutrophil decrease in 9 TAVALISSE-treated patients (no placebo-treated patients). Dose interruption or reduction was required in 4 patients and study drug discontinuation in 1 patient.

Patients with neutropenia may be more susceptible to infections. Monitor ANC monthly, and monitor for infection during treatment. Manage toxicity with TAVALISSE interruption, reduction or discontinuation [see *DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment*].

Hepatic

Drug-related hepatic disorder events, mainly elevated transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), occurred in 16% of patients receiving TAVALISSE (alanine aminotransferase increased in 11%, aspartate aminotransferase increased in 9% of TAVALISSE-treated patients, with some patients experiencing both) (2% of placebo-treated patients). Drug-related hepatic disorder events were mild in 10% and moderate in 6% of TAVALISSE-treated patients.

Laboratory testing showed maximum AST and /or ALT levels more than 3 × the upper limit of normal (ULN) in 9% of patients receiving TAVALISSE (no placebo-treated patients). [see ADVERSE REACTIONS*Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data*]

Elevated transaminases associated with TAVALISSE led to dose reduction or interruption in 6 patients and discontinuation in 1 patient. Elevated transaminases recovered to baseline levels within 6 weeks of onset.

Monitor liver function tests monthly during treatment. If ALT or AST increase more than 3 × ULN, interrupt, reduce or discontinue TAVALISSE to manage elevated transaminases.

TAVALISSE may be associated with hyperbilirubinemia, particularly in patients with genetic polymorphisms of UGT1A1 (Gilbert's genotype); these patients should be monitored frequently. Discontinue treatment if concomitant total bilirubin increase is greater than 2 × ULN [see *DOSAGE AND ADMINISTRATION*].

Immune

Infections

Infections were reported in 30% of patients (23% mild, 6% moderate, 2% severe, 2% serious) treated with TAVALISSE (20% of placebo-treated patients, including 2% serious), mostly pneumonia and respiratory tract infections. Serious events included bronchitis and pneumonia. One patient discontinued TAVALISSE due to pneumonia. The benefit risk of continuing therapy during an infection should be evaluated by the Prescriber.

Monitoring and Laboratory Tests

After obtaining baseline assessments, monitor:

- complete blood counts (CBCs), including platelet counts, monthly until a stable platelet count (at least 50 × 10^9 /L) is achieved. Thereafter, continue to monitor CBCs, including neutrophils, regularly.
- liver function tests (LFTs) (ALT, AST, and bilirubin) monthly.
- blood pressure every 2 weeks until establishment of a stable dose, then monthly thereafter.

Sexual Health

Reproduction

TAVALISSE is contraindicated during pregnancy. Although there is insufficient data on the use of TAVALISSE during pregnancy, studies in animals show reproductive toxicity [see *Special Populations* and *NON-CLINICAL TOXICOLOGY]*. Advise patients of potential risk to a fetus. Women of childbearing potential must use effective contraception during treatment and at least one month after the last dose and verify pregnancy status prior to initiating TAVALISSE.

Fertility

There are no data on the effect of TAVALISSE on human fertility. Based on the finding of reduced pregnancy rates in animal studies, TAVALISSE may affect female fertility [see *Special*

Populations].

7.1 Special Populations

7.1.1 Pregnant Women

Fostamatinib is contraindicated during pregnancy.

TAVALISSE was shown in reproductive toxicology studies to cause fetal resorption and to have various teratogenic effects [see *NON-CLINICAL TOXICOLOGY*]. Thus, the eligibility criteria of these studies excluded patients who were pregnant, attempting to conceive, or lactating; strict contraception guidelines were enforced throughout all studies.

Pregnancies occurring during clinical trials resulted in stillbirth/spontaneous abortion or miscarriages as well as healthy newborns. For females of reproductive potential, verify pregnancy status prior to initiating TAVALISSE.

7.1.2 Breast-feeding

There are no data on the presence of fostamatinib and/or its metabolites in human milk, the effects on the breastfed child or on milk production. In rodents, R406 (the major active metabolite) was detected in maternal milk at concentrations 5- to 10-fold higher than in maternal plasma. Because of the potential for serious adverse reactions in a breastfed child from TAVALISSE, women should not breast-feed during treatment with TAVALISSE and for at least 1 month after the last dose.

7.1.3 Pediatrics

Safety and effectiveness in pediatric patients have not been established. TAVALISSE is not indicated for use in patients less than 18 years of age and young adults until growth is complete because adverse effects on actively growing bones were observed in non-clinical studies. In sub-chronic, chronic, and carcinogenicity studies of TAVALISSE, chondrodystrophy of the femoral head was seen in rodents. In a study in juvenile rabbits, growth plate dysplasia was observed in the proximal femur and femoro-tibial joint, and bone marrow cellularity was reduced in the femur and sternum.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age):

TAVALISSE was received by 28 (28%) patients ≥65 and 11 (11%) patients ≥75 years of age. The incidence of adverse events was higher in the geriatric population (93% in patients ≥ 65 years of age and 80% in patients < 65 years of age).

Patients ≥ 65 years of age had more serious adverse events than patients <65 years of age [6 (21%) patients vs 7 (9%) patients], adverse events leading to discontinuation [5 (18%) patients vs 5 (7%) patients], and hypertension [11 (39%) TAVALISSE and 2 (18%) placebo patients ≥ 65 years of age vs 17 (23%) TAVALISSE and 4 (11%) placebo patients <65 years of age].

No overall differences in effectiveness were observed in these patients compared to younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following clinically important adverse reactions can become serious: hypertension, hepatotoxicity, diarrhea and neutropenia [see *WARNINGS AND PRECAUTIONS*].

The most common adverse reactions associated with TAVALISSE in the ITP placebo-controlled studies were diarrhea, hypertension, nausea, epistaxis, dizziness, and alanine aminotransferase increased.

Serious adverse reactions associated with TAVALISSE included febrile neutropenia, diarrhea, pneumonia, and hypertensive crisis (1% of patients each).

Severe adverse reactions in patients receiving TAVALISSE included dyspnea and hypertension (2% each), neutropenia, chest pain, diarrhea, dizziness, pneumonia, and hypoxia (all 1%).

Adverse reactions that led to drug withdrawal in patients receiving TAVALISSE included pneumonia, alanine amino transferase, diarrhea, chest pain, abdominal pain, and neutropenia.

Adverse reactions leading to drug interruption in more than 1 patient receiving TAVALISSE were ALT increased, diarrhea, and influenza-like illness.

Adverse reactions leading to dose reduction in more than 1 patient receiving TAVALISSE were diarrhea and hypertension.

Many adverse reactions associated with TAVALISSE were manageable with dose reduction/interruption and medication [see *WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION*].

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety profile of TAVALISSE is based on 2 Placebo-Controlled Phase 3 studies (C788-047 and C788-048) and one Phase 3 open-label extension study (C788-049). A total of 150 patients (102 TAVALISSE, 48 placebo) received study drug in the 2 Placebo-Controlled studies. Median duration of exposure to fostamatinib and placebo was similar between the 2 treatment groups.

Table 4 presents the drug-related adverse events reported in at least 2% of TAVALISSE-treated patients and reported more frequently than in placebo patients in the Placebo-Controlled Period.

Table 4 Drug-Related Adverse Events reported in ≥2% of TAVALISSE-treated patients and that were reported more frequently than in placebo patients - Placebo-Controlled Period

System Organ Class/ Preferred Term	TAVALISSE 100 mg BID* N=102 n (%)	Placebo N = 48 n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Neutropenia**	7 (6.9)	0 (0.0)
Leukopenia	2 (2.0)	0 (0.0)
CARDIOVASCULAR DISORDERS		
Tachycardia	3 (2.9)	0 (0.0)
GASTROINTESTINAL DISORDERS		
Diarrhea**	32 (31.4)	7 (14.6)
Nausea	19 (18.6)	4 (8.3)
Abdominal pain**	7 (6.9)	2 (4.2)
Flatulence	5 (4.9)	0 (0.0)
Constipation	3 (2.9)	1 (2.1)
Dyspepsia	3 (2.9)	1 (2.1)
Abdominal distension	2 (2.0)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Chest Pain	6 (5.9)	1 (2.1)
Fatigue	6 (5.9)	1 (2.1)
Influenza-like illness	3 (2.9)	0 (0.0)
Oedema peripheral	3 (2.9)	0 (0.0)
Chills	2 (2.0)	0 (0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Contusion	6 (5.9)	0 (0.0)
INVESTIGATIONS		
Alanine Aminotransferase Increased	11 (10.8)	0 (0.0)
Aspartate Aminotransferase Increased	9 (8.8)	0 (0.0)
Blood bilirubin increased	2 (2.0)	0 (0.0)
Blood lactate dehydrogenase increased	2 (2.0)	0 (0.0)
METABOLISM AND NUTRITION DISORDERS		
Decreased appetite	2 (2.0)	0 (0.0)

System Organ Class/ Preferred Term	TAVALISSE 100 mg BID* N=102 n (%)	Placebo N = 48 n (%)
MUSCLOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Myalgia	2 (2.0)	0 (0.0)
NERVOUS SYSTEM DISORDERS		
Dizziness	11 (10.8)	4 (8.3)
Dysgeusia	4 (3.9)	0 (0.0)
Memory impairment	2 (2.0)	0 (0.0)
PSYCHIATRIC DISORDERS		
Insomnia	3 (2.9)	0 (0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL		
Epistaxis	16 (15.7)	5 (10.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	8 (7.8)	1 (2.1)
Blood blister	2 (2.0)	0 (0.0)
Hair colour changes	2 (2.0)	0 (0.0)
VASCULAR DISORDERS		
Hypertension**	28 (27.5)	6 (12.5)

*All patients initially received study drug at 100 mg twice daily (or matching placebo). Nearly 90% of patients were dose escalated to 150 mg twice daily (or matching placebo) based on platelet count and tolerability at Week 4 or later.

** Includes multiple adverse event terms

8.3 Less Common Clinical Trial Adverse Reactions

The list below represents the drug-related adverse events reported in less than 2% of TAVALISSE-treated patients in the Placebo-Controlled Period.

Blood and Lymphatic System Disorders: leukocytosis, thrombocytosis

Ear and Labyrinth Disorders: vertigo

Eye Disorders: blepharitis

Gastrointestinal Disorders: eructation, gastritis, gastrointestinal disorder, gastroesophageal reflux disease, hemorrhoids, oesophageal pain, retching

Infections and Infestations: bacteriuria, oral candidiasis, pneumonia

Investigations: blood alkaline phosphatase increased, liver function test abnormal, weight decreased

Musculoskeletal and Connective Tissue Disorders: joint swelling

Nervous System Disorders: disturbance in attention, hypogeusia, lethargy

Psychiatric Disorders: restlessness

Renal and Urinary Disorders: leukocyturia

Respiratory, Thoracic and Mediastinal Disorders: dry throat, dysphonia, hypoxia

Skin and Subcutaneous Tissue Disorders: actinic keratosis, alopecia, dry skin, erythema, nail disorder, photosensitivity reaction, pruritus

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Changes in ALT, AST and Absolute Neutrophil Counts from baseline to post-treatment study assessment have been identified during TAVALISSE clinical trials (See Table 5).

Table 5 Selected Laboratory Abnormalities (ALT, AST, ANC) at the Post-treatment Evaluation in Placebo-Controlled Trials

Laboratory Parameter	TAVALISSE 100 mg BID* (N = 102) n (%)	Placebo (N = 48) n (%)
Alanine aminotransferase (ALT)**		
≥ 3.0 and < 5 x ULN	3 (3)	0
≥ 5.0 and < 10 x ULN	5 (5)**	0
≥ 10.0 x ULN	1 (1)**	0
Absolute neutrophil count (ANC)		
Grade 3 (≥ 0.5 to < 1.0 x 10^3)	2 (2)	0
Grade 4 (< 0.5 x 10^3)	0	0

*All patients initially received study drug at 100 mg twice daily (or matching placebo). Nearly 90% of patients were dose escalated to 150 mg twice daily (or matching placebo) based on platelet count and tolerability at Week 4 or later.
** One patient each in the indicated ALT categories also had AST elevations, which were the only AST elevations observed

8.5 Clinical Trial Adverse Reactions (Pediatrics)

TAVALISSE has not been studied in the pediatric population.

8.6 Post-Market Adverse Reactions

No new, clinically significant, adverse reactions have been reported from post-marketing experience to date.

9 DRUG INTERACTIONS

9.2 Overview

Concomitant use with strong cytochrome P450 (CYP) 3A4 inhibitors increases exposure to R406 (the major active metabolite), which may increase the risk of adverse reactions. Monitor

for toxicities of TAVALISSE that may require dose reduction (see Table 1) when given concurrently with a strong CYP3A4 inhibitor [see *DOSAGE AND ADMINISTRATION* and *ACTION AND CLINICAL PHARMACOLOGY*].

Concomitant use with a strong CYP3A4 inducer reduces exposure to R406. Concomitant use of TAVALISSE with strong CYP3A4 inducers is not recommended [see *ACTION AND CLINICAL PHARMACOLOGY*].

Concomitant use of TAVALISSE may increase concentrations of some CYP3A4, breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) substrate drugs. Monitor for toxicities of these substrate drugs that may require dosage reduction when given concurrently with TAVALISSE.

No studies have been performed examining the effect of ethyl alcohol on the pharmacokinetic parameters of R406. From the understanding of TAVALISSE metabolism, a direct interaction between alcohol and R406 appears unlikely.

No significant interactions were seen with concomitant use of TAVALISSE with the following drugs: methotrexate (OAT1/3 transporters), pioglitazone (CYP2C8 substrate) and ranitidine (H_2-antagonist that increases gastric pH). Concomitant use of TAVALISSE was shown to slightly increase the exposure of the following drugs: midazolam (CYP 3A4 substrate) - single dose 7.5 mg with fostamatinib 100 mg administered bid increased midazolam AUC by 23% and C_{max} by 9%, hormonal contraceptive containing 0.03 mg ethinylestradiol with fostamatinib 100 mg administered bid increased AUC by 28% and C_{max} by 34% of ethinylestradiol, and verapamil (moderate CYP3A4 inhibitor) - use of verapamil 80 mg three times daily for 4 days with a single dose of 150 mg fostamatinib increased R406 AUC by 39% and C_{max} by 6%. The observed changes in exposure are not expected to be clinically significant.

Effect on warfarin

Since SYK-inhibition may have potential effects on platelet aggregation, anticoagulant activity (e.g. INR) where relevant should be monitored when anticoagulants with narrow therapeutic index such as warfarin, are co-administered with fostamatinib.

Bradycardic or PR interval-prolonging agents

TAVALISSE has a mild heart rate lowering effect and prolongs the uncorrected PR interval [see WARNINGS AND PRECAUTIONS*, Heart rate and Conduction Abnormalities and* ACTION AND CLINICAL PHARMACOLOGY*, Cardiac Electrophysiology*]. The use of TAVALISSE with bradycardic or PR interval-prolonging agents should be carefully considered to determine whether the therapeutic benefit outweighs the potential risk in patients with very low heart rate.

Additional Potential Drug Interactions based on in vitro data:

UGT1A1 substrates/UGT1A1 inhibitors: Based on the *in vitro* data, R406 was identified as a potent UGT1A1 inhibitor, suggesting that its effect on UGT1A1-mediated bilirubin glucuronidation may be responsible for the increase in unconjugated bilirubin levels observed in some patients receiving fostamatinib (TAVALISSE). Patients should be monitored for toxicity for drugs that are metabolized extensively by UGT1A1.

9.3 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 6 Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
P-gp substrate (e.g. digoxin)	CT	Concomitant use of digoxin (0.25 mg once daily) with 100 mg twice daily TAVALISSE increased digoxin AUC by 37% and C_{max} by 70%	Monitor for toxicities of the P-gp substrate drug that may require dosage reduction when given concurrently with TAVALISSE.
BCRP substrates (e.g. rosuvastatin)	CT	Concomitant use of rosuvastatin (single dose 20 mg) with 100 mg twice daily TAVALISSE increased rosuvastatin AUC by 95% and C_{max} by 88%	Monitor for toxicities of BCRP substrate drug that may require dosage reduction when given concurrently with TAVALISSE.
CYP3A4 substrates (e.g. simvastatin)	CT	Concomitant use of simvastatin (single dose 40 mg) with 100 mg twice daily TAVALISSE increased simvastatin AUC by 64% and C_{max} by 113% and simvastatin acid AUC by 66% and C_{max} by 83%	Monitor for toxicities of CYP3A4 substrate drug that may require dosage reduction when given concurrently with TAVALISSE.
Strong CYP3A4 inhibitor (e.g. ketoconazole)	CT	Concomitant use of ketoconazole (200 mg twice daily for 3.5 days) with a single dose of 80 mg TAVALISSE (0.53 times the 150 mg dosage) increased R406 AUC by 102% and C_{max} by 37%	Monitor for toxicities of TAVALISSE that may require dose reduction (see Table 1) when given concurrently with a strong CYP3A4 inhibitor.

Common name	Source of Evidence	Effect	Clinical comment
Strong CYP3A4 inducers (e.g., rifampin/rifampicin)	CT	Concomitant use of rifampicin (600 mg once daily for 8 days) with a single dose of 150 mg TAVALISSE decreased R406 AUC by 75% and C_{max} by 59%	Concomitant use of TAVALISSE with strong CYP3A4 inducers is not recommended.

Legend: BCRP = breast cancer resistance protein; C = Case Study; CT = Clinical Trial; CYP = cytochrome P450; P-gp = P-glycoprotein; T = Theoretical

Other medicinal products with strong CYP3A4 inhibition potential when coadministered with TAVALISSE are: boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir.

9.4 Drug-Food Interactions

Administration of TAVALISSE with a high-calorie, high-fat meal (deriving approximately 150, 250, and 500–600 calories from protein, carbohydrate, and fat, respectively) increased R406 AUC by 23% and C_{max} by 15%, indicating fostamatinib can be administered with or without food [see *DOSAGE AND ADMINISTRATION*].

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Fostamatinib is a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase (SYK). The major metabolite of fostamatinib, R406, inhibits signal transduction of Fc-activating receptors and B-cell receptor. The fostamatinib metabolite R406 reduces antibody-mediated destruction of platelets.

10.2 Pharmacodynamics

Over the range of doses studied in healthy subjects, the effect of R406 on mean treatment-related increases on blood pressure appeared to be dose-dependent and variable among subjects. The blood pressure effects generally resolved within a week of discontinuing treatment.

Cardiac Electrophysiology

In a randomized, blinded, placebo- and positive-controlled four-arm parallel group ECG assessment study, 208 healthy subjects (N=51-53/treatment group) were randomized to receive TAVALISSE 100 mg bid or TAVALISSE 300 mg bid for four days. ECG assessments were performed prior to and on Day 4 of treatment.

No clinically significant effect on the QTcF interval was observed in the TAVALISSE 100 mg and 300 mg bid groups.

Fostamatinib was associated with a mild reduction in heart rate and prolongation of the uncorrected PR interval. After correction for heart rate, there was no significant PR prolongation. The maximum difference from placebo in mean change from baseline heart rate was -3.99 bpm (90% CI -6.00, -1.98) in the 100 mg bid group and -6.64 bpm (90% CI -8.64, -4.64) in the 300 mg bid group, both at 3.5 h. The maximum difference from placebo in mean change from baseline in uncorrected PR interval was 5.19 ms (90% CI 2.34, 8.03) in the 100 bid mg group and 9.23 ms (90% CI 6.4, 12.06) in the 300 mg bid group, both at 3 h.

10.3 Pharmacokinetics

TAVALISSE is a prodrug that is converted in the gut to the major active metabolite, R406. In healthy subjects, after a single 150 mg oral dose of fostamatinib, mean (± standard deviation [SD]) exposure estimates of R406 are 550 (± 270) ng/mL for C_{max} and 7080 (± 2670) ng·h/mL for AUC. R406 pharmacokinetics is linear and exposure is approximately dose-proportional up to 200 mg bid (1.3 times the 150 mg dosage). R406 accumulates approximately 2- to 3-fold upon twice daily dosing at 100-160 mg (0.67 to 1.06 times the 150 mg dosage).

Study C788-049 is a Phase 3 open-label extension study of fostamatinib disodium (TAVALISSE) in the treatment of persistent/chronic ITP. During Month 2 (Visit 3), a subset of 12 patients receiving 150 mg twice daily TAVALISSE participated in the PK portion of the study. They remained at the clinic for up to 9 hours during the visit, and blood samples were collected over an 8-hour period at the following timepoints: pre-dose and 0.5, 1, 2, 4, 6, and 8 hours post-dose. Plasma samples were analysed for R406.

Table 7 Steady-State Plasma R406, Pharmacokinetic Parameters in ITP patients

TAVALISSE Dose (*bid*)	N	C_{max} (ng/mL)	AUC_{0-8} (ng•h/mL)	AUC_{0-12} (ng•h/mL)	AUC_{0-ss} (ng•h/mL)
150 mg	12	810 ± 289	4340 ± 1640	5450 ± 2210	11,000

Data presented as average C_{max} and average AUC_{0-8}
AUC_{0-12} and AUC_{0-ss} are based on estimates

Absorption: After oral administration of TAVALISSE, the absolute bioavailability of R406 was 55% with high variability (range 30 – 85 %). The median t_{max} of R406 is approximately 1.5 hours (range: 1 to 4 hours). Negligible levels of fostamatinib were found in plasma.

Effect of Food

Administration of TAVALISSE with a high-calorie, high-fat meal (deriving approximately 150, 250, and 500–600 calories from protein, carbohydrate, and fat, respectively) increased R406 AUC by 23% and C_{max} by 15% [see *DOSAGE AND ADMINISTRATION*].

Distribution: In *in vitro* studies, R406 is 98.3% protein bound in human plasma. The red blood cell to plasma concentration ratio is approximately 2.6. The mean (± SD) volume of distribution

at steady-state of R406 is 256 (± 92) L.

Metabolism: TAVALISSE is metabolized in the gut by alkaline phosphatase to the major active metabolite, R406. R406 is extensively metabolized, primarily through pathways of CYP450-mediated oxidation (by CYP3A4) and glucuronidation (by UDP glucuronosyltransferase [UGT]1A9). R406 is the predominant moiety in the systemic circulation, and there was minimal exposure to any R406 metabolites.

Elimination/Excretion: The mean (± SD) terminal half-life of R406 is approximately 15 (± 4.3) hours. Following an oral dose of TAVALISSE, approximately 80% of the R406 metabolite is excreted in feces with approximately 20% excreted in the urine. The major component excreted in urine was R406 N-glucuronide. The major components excreted in feces were R406, *O*-desmethyl R406 and a metabolite produced by gut bacteria from the *O*-desmethyl metabolite of R406.

Trace amounts of R406 (major metabolite of TAVALISSE) were detected in semen samples of healthy men administered fostamatinib (150mg).

Special Populations and Conditions

Geriatrics: In the placebo-controlled studies, TAVALISSE was received by 28 patients ≥65 and 11 patients ≥75 years of age. Population pharmacokinetic analysis did not identify age as a significant covariate affecting the exposure to R406.

Sex: In clinical pharmacology studies, female subjects exhibited higher R406 exposure than males; however, population pharmacokinetic analysis indicated that when exposure estimates were adjusted to body weight, the gender difference disappeared. R406 exposure is expected to be relatively higher in a lower weight individual irrespective of sex.

Pregnancy and Breast-feeding: The distribution of R406 into breast milk has not been assessed in humans. In rats, R406 was found in maternal milk in concentrations higher than that found in maternal plasma. The milk to plasma ratio of R406 was determined to be approximately 5.5 to 9.9 fold.

Ethnic origin: Population pharmacokinetic analysis did not identify race/ethnicity as a significant covariate affecting the exposure to R406.

Hepatic Insufficiency: In a dedicated hepatic impairment study, no significant relationship was detected between Child-Pugh scores (Child-Pugh Class A, B and C) and pharmacokinetic parameters of TAVALISSE. TAVALISSE should not be used in patients with severe hepatic impairment.

Renal Insufficiency: R406 exposure is not increased in patients with renal impairment (creatinine clearance [CL_{cr}] ≥ 30 to < 50 mL/min, estimated by Cockcroft Gault equation and end stage renal disease requiring dialysis)

Obesity: Population pharmacokinetic analysis found body weight to be a significant covariate affecting the exposure to R406. Exposure decreases with increasing body weight. There was no adjustment of TAVALISSE dose based on body weight during the clinical development program.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C). Store in the original package to protect from moisture. Keep the bottle tightly closed. Do not remove desiccant canisters.

Keep out of the sight and reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

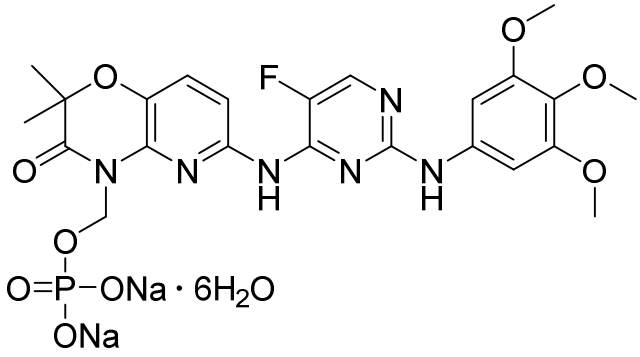
Common name: Fostamatinib disodium hexahydrate

Chemical name: disodium (6-[[5-fluoro-2-(3,4,5-trimethoxyanilino) pyrimidin-4-yl]amino]-2,2-dimethyl-3-oxo-pyrido[3,2-b][1,4]oxazin-4-yl)methyl phosphate hexahydrate

Molecular formula: $C_{23}H_{24}FN_6Na_2O_9P \cdot 6H_2O$

Molecular mass: 732.52

Structural formula:



Physicochemical properties: TAVALISSE is formulated with the disodium hexahydrate salt of fostamatinib, a phosphate prodrug that converts to its pharmacologically active metabolite, R940406 (R406), *in vivo*.

Fostamatinib disodium is a white to off-white powder that is practically insoluble in pH 1.2 aqueous buffer, slightly soluble in water, and soluble in methanol.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 8 Summary of patient demographics for clinical trials in ITP

Study #	Trial design	Dosage, route of administration and duration	Study patients (n=number)	Mean age (Range)	Sex
FIT-1 (C788-047)	Phase 3, randomized, double-blind, placebo-controlled, parallel group study	Fostamatinib 100 mg or matching Placebo; Oral *bid* for 4 weeks; then 150 mg *bid* for remainder of study (24 weeks)	N=76 Fostamatinib: 51 Placebo: 25	56.0 years (20-88)	Female 47 (61.8%) Male 29 (38.2%)
FIT-2 (C788-048)	Phase 3, randomized, double-blind, placebo-controlled, parallel group study	Fostamatinib 100 mg or matching Placebo; Oral *bid* for 4 weeks; then 150 mg *bid* for remainder of study (24 weeks)	N= 74 Fostamatinib: 50 Placebo: 24	49.2 years (20-82)	Female 44 (59.5%) Male 30 (40.5%)
FIT-3 (C788-049)	Phase 3, open-label extension study	(Responder): Fostamatinib 100 mg; Oral *bid* for 4 weeks; then 150 mg *bid* for remainder of study (2 years) (Non-responder): Fostamatinib 100 mg; Oral *bid* for 4 weeks; then 150 mg *bid* for remainder of study (2 years)	N=123	51.8 years (20-88)	Female 74 (60.2%) Male 49 (39.8%)

TAVALISSE was studied in two identical, double-blind, placebo-controlled efficacy and safety studies [FIT-1 (C788-047) and FIT-2 (C788-048)], and in an open-label extension study FIT-3 (C788-049).

A total of 150 patients with persistent (7%) or chronic ITP (93%), who had an insufficient response to previous treatment (which included corticosteroids, immunoglobulins, splenectomy, and/or a thrombopoietin receptor agonist) were enrolled. For each study, patients were

randomized 2:1 to TAVALISSE or placebo for 24 weeks; groups were stratified with respect to prior splenectomy and severity of thrombocytopenia. Stable concurrent ITP therapy (glucocorticoids [< 20 mg prednisone equivalent per day], azathioprine, or danazol) was allowed, and rescue therapy was permitted.

All patients initially received study drug at 100 mg twice daily (or matching placebo). Based on platelet count and tolerability, dose escalation to 150 mg twice daily (or matching placebo) was undertaken in 88% of patients at Week 4 or later. Patients who did not respond to treatment after 12 weeks, as well as patients who completed the 24-week double-blind study, were eligible to enroll in open-label extension study (FIT-3).

The most common prior ITP treatments included corticosteroids (94%), immunoglobulins (53%), and thrombopoietin receptor agonists (TPO-RA) (47%), and 35% had undergone splenectomy. Median time since ITP diagnosis was 8.5 years. At baseline, the median platelet count was 16×10^9/L (with 45% less than 15×10^9/L) and 47% were on stable ITP therapy.

The efficacy of TAVALISSE was based on the primary endpoint of stable platelet response (at least 50×10^9/L on at least 4 of the 6 visits between Weeks 14 to 24).

Patients from FIT-1 and FIT-2 who completed 24 weeks of treatment, or who did not respond to treatment after 12 weeks, were eligible to enroll in FIT-3, an open-label extension study with primary objective to assess safety. Of 123 enrolled patients, 44 patients were previously randomized to placebo and 79 patients were previously randomized to TAVALISSE.

Patients remained blinded to their treatment assignment from the previous study (TAVALISSE or placebo), so their starting dose in this study was based on their final platelet count. Patients designated as responders at the time of roll over continued in the extension study at their current trial dose and regimen. Patients who entered the extension study as non-responders received TAVALISSE 100 mg twice daily regardless of their dose and regimen in the prior study.

For the FIT-3 trial, stable response was prospectively defined as no 2 visits, at least 4 weeks apart, with a platelet count less than 50×10^9/L, without an intervening visit with a platelet count of at least 50×10^9/L (unrelated to rescue therapy), within a period of 12 weeks following initial achievement of the target platelet count. Eighty-one of the 123 patients (66%) have discontinued from the study early.

14.2 Study Results

Randomized, Placebo-Controlled Studies

Study outcomes for FIT-1 (C788-047) and FIT-2 (C788-048) are shown in Table 9.

Table 9 Study Outcomes from Placebo-Controlled Clinical Studies in ITP

Study Outcomes	Study FIT-1		Study FIT-2	
	TAVALISSE (N=51)	Placebo (N=25)	TAVALISSE (N=50)	Placebo (N=24)
	n (%)	n (%)	n (%)	n (%)
Stable platelet response[1,2]	9 (18)	0 (0)	9 (18)	1 (4)
	$p^3 = 0.03$		NS	
Rolled-over into FIT-3 at Week 12	28 (55)	22 (88)	33 (66)	19 (79)
Completed study (Week 24)	12 (24)	1 (4)	13 (26)	2 (8)

[1] Includes all patients with platelet counts and excludes patients whose platelet counts were measured following rescue therapy after Week 10
[2] Stable platelet response was prospectively defined as a platelet count of at least 50×10^9 /L on at least 4 of the 6 visits between Weeks 14 and 24
[3] p-value from Fisher Exact test
NS = Did not demonstrate a statistically significant difference between treatment arms

In the FIT-1 and FIT-2 studies, a total of 46 patients in the TAVALISSE arm had received a prior TPO-RA treatment; among these patients, 7 patients (15%) achieved a stable response to TAVALISSE. All 7 patients had previously discontinued TPO-RA due to loss of effect. Among TAVALISSE patients who were stable responders, the median platelet count increased to 95×10^9 /L across post-baseline visits with a maximum of 254.5×10^9 /L. Rescue medication was required by 30% and 45% of patients receiving TAVALISSE or placebo, respectively.

During the placebo-controlled studies, bleeding events occurred in 29% and 37% of patients in the TAVALISSE and placebo arms, respectively.

Bleeding-related adverse events (AEs) were reported as serious in 4% of TAVALISSE-treated patients (10% placebo), severe in 1% of TAVALISSE-treated patients (6% placebo), and moderate in 9% of TAVALISSE-treated patients (10% placebo). All severe bleeding events led to hospitalizations.

Extension Study

Placebo Crossover: In a prospectively defined analysis, the 44 patients treated with placebo in the prior study were evaluated for stable response for TAVALISSE (from the first 24 weeks of the study) with their placebo data as the comparator for this objective measure). Ten of these patients (22.7%) (including a single patient who was a placebo responder in the prior study) met the criteria for stable response. Thus, the difference in response from TAVALISSE compared with placebo was 20.5% (95% CI = 8.5-32.4).

Extension: Among the patients who achieved stable response during the FIT-1, FIT-2 and FIT-3 trials, 18 patients maintained the platelet count of at least 50×10^9 /L for 12 months or longer.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In a number of non-clinical toxicology studies, exposure to R406 (AUC_{0-24h}), the active metabolite of fostamatinib, was found to be higher in females as compared to males, with the female/male AUC ratio ranging from 0.9 up to 1.4 at the highest dose level of 60 mg/kg (2.1 times the estimated human exposure at a clinical dose of 300 mg fostamatinib). Lower levels of food consumption and decrease in body weight (particularly females) were also noted as part of toxicological assessment in rodents subject to fostamatinib/R406 administration at various doses.

No single-dose toxicity studies were conducted. Consistently, in the chronic and sub-chronic toxicity and carcinogenicity studies, rats and monkeys given doses up to and including 100 mg/kg/day fostamatinib, developed reversible findings of moderate marrow hypocellularity, a reduction in peripheral blood lymphocyte count (rats more marked) and mild effects on other hematological parameters. Reduced organ weights including spleen, thymus, kidneys, pituitary, thyroid and parathyroids and statistically significant elevations in liver enzymes (ALP, ALT, GLDH and AST) were also observed, at doses above the reported NOAELs of 0.2 – 1.8 times the estimated human exposure at 300 mg fostamatinib.

Decreases in spleen weights were sometimes accompanied with minimal centrilobular hypertrophy, minimal to mild bone marrow and lymphoid depletion. Dose-dependent increase in severity of angiectasis/cystic degeneration of the adrenal gland and generalized vacuolar changes of the adrenal cortex (cortex and/or medulla; predominantly in females), a known and common age-related change in rats, were also reported in a 104 week and 13/ 26-week repeat dose toxicity studies of fostamatinib in rats.

Chondrodystrophy of the femoral head was observed in some animals in the highest dose groups in 2 fostamatinib 4-week rat studies (with the calcium and sodium salts), and was not fully reversible by the end of the recovery period.

In a 1-month study in juvenile rabbits, findings were consistent with those seen in the general toxicity studies. Fostamatinib produced growth plate dysplasia in the proximal femur and femoro-tibial joint and reduced bone marrow cellularity in the femur and sternum at 30 and 60 mg/kg/day (2.4 – 5.0 times the estimated human exposure at a dose of 300 mg fostamatinib). Significantly increased levels of bilirubin (3-5 fold), urea (19-21%; females only) and slightly decreased inorganic phosphate (9% reduction) at some or all dose levels were also reported in juvenile rabbits.

Carcinogenicity

Fostamatinib was not carcinogenic in a 2-year study in mice when administered daily by oral gavage at doses up to 500/250 mg/kg/day and was not carcinogenic in rats when administered by oral gavage at 45 mg/kg/day.

Genotoxicity

Fostamatinib and its major active metabolite (R406) were not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay or an *in vivo* mouse bone marrow micronucleus assay.

Immunotoxicity

Immunophenotyping in rats revealed a reduction in various subtypes of lymphocytes found in peripheral blood, bone marrow, spleen, and the thymus.

Cardiac Safety

In a dedicated primate cardiovascular safety pharmacology study, employing a Latin Square design, ECGs were collected at 30-minute intervals from -30 minutes to 360 minutes after dosing, at dose levels as high as 50 mg/kg (average exposure 1910 ng/mL at 6-hour timepoint).

Heart rate reduction was observed by 16% and 20% (maximum recording was a reduction of 29 bpm) at 50 mg/kg at 150 and 180 minutes respectively. Administration of 50 mg/kg R940406 besylate tended to increase RR interval by approximately 17% and 20% at 150 and 180 min post-dose, respectively, when compared to vehicle. A maximal increase of approximately 91.3 ms was noted 180 min post-dose. There were no abnormal clinical observations and/or effect on systolic, diastolic, or mean arterial blood pressure. There were also no marked effects on PR, QT, QTcF, QTcQ intervals or QRS duration, and no abnormalities in gross morphology or rhythm of the ECG.

Electrocardiographic measurements were also performed in 36 adult male and 36 adult female conscious Cynomolgus monkeys enrolled in a 9-month repeat dose oral toxicity study. The animals were exposed to daily oral doses of fostamatinib up to 60 mg/kg/day (reduced after 13 weeks to 34 mg/kg/day due to generalized toxicity). Electrocardiographic measurements and observations made pre-treatment to exposure, as well as on weeks 6, 13, 26, 39 and 22 days after week 39 (recovery), revealed no clinically significant differences in ECG intervals or waveform anomalies associated with any of the repeat doses of R935788 sodium salt.

In pharmacology studies in male rats, statistically significant but reversible blood pressure increases were observed even at the lowest dose levels (8.5 mg/kg or 10 mg/kg) of fostamatinib administered in these studies. The EC50 for mean arterial, systolic and diastolic blood pressure was estimated to be in the range of 0.7 to 1 µmol/L (320 to 450 ng/mL).

A marginal reduction in heart rate, as well as prolongation of PR and QA intervals, at the high dose (100 mg/kg/day), were also observed in the 28-day pharmacology study in rats.

Bone remodelling

Increases in the incidence of impaired limb function accompanied by chondrodystrophy/degenerative joint disease of the femoral head and thickening of the epiphyseal growth plate were noted in a 1-month study in juvenile rabbits as well as in the sub-chronic, chronic, and carcinogenicity studies of fostamatinib in rodents. The finding was especially observed in actively growing bone. Safety margins based on the animal data ranged from 1.6 - 9.3 times the estimated human exposure at the maximum clinical dose of 300 mg fostamatinib. Microscopically, the thickening of growth plates was characterized by increased numbers of hypertrophic chondrocytes resulting in an expansion of the zone of hypertrophy, characterized as likely due to inhibition of angiogenesis.

The inhibitory effects of R406, the active metabolite of fostamatinib, on osteoclastogenesis and bone resorptive capacity were confirmed *in vitro*.

Reproductive and Developmental Toxicology

In a fertility study with oral fostamatinib, all mating (e.g., time to mating, breeding proficiency), sperm assessments (e.g., number and motility), and organ weight (e.g., paired testis weight) parameters in male rats were unaffected by dosages as high as 40 mg/kg/day or 1.8 times the estimated human exposure at 300 mg fostamatinib dose. Reductions in the weight of the uterus was observed in female rats treated with fostamatinib in the 4-week but not in the 13- and 26-week repeat dose toxicity study. Increased degenerate/necrotic ovarian follicles were noted in female juvenile rabbits, a finding which may be explained by the anti-angiogenic effect of

fostamatinib.

In embryo-fetal development studies, pregnant animals were orally administered fostamatinib during the period of organogenesis at doses up to 25 and 50 mg/kg/day in rats and rabbits, respectively. The adverse developmental outcomes included a statistically significant increase in embryo-fetal mortality (post-implantation loss), alterations to growth (lower fetal weights), and percentage of nonviable embryos per litter. Fetal malformations were also reported, predominantly affecting the kidneys (absent kidneys, malpositioned, malrotated, fused) and associated tissues/organs (absent or dilated ureters, uteri, and vas deferens) as well as vessel development from the aorta (absence of the innominate artery, and retroesophageal subclavian artery). These effects are consistent with known targets of fostamatinib, including SYK (target), VEGFR-2 (off target) and RET-kinase (off target).

These effects occurred at maternal exposures (AUCs) of 3,763 ng·h/mL in rats and 111,105 ng·h/mL in rabbits, or 0.4 and 1.8 times the estimated maximum daily clinical human exposure to fostamatinib, respectively.

In a peri and postnatal development study in rats, fostamatinib was orally administered at doses of 2.5, 12.5, and 25 mg/kg/day from gestation day 7 until lactation day 20. The dose of 25 mg/kg/day was associated with maternal toxicity, including decreased body weight gains and food consumption. At doses as low as 12.5 mg/kg/day fostamatinib (or 0.5 times the estimated maximum daily fostamatinib human exposure dose level) caused increases in newborn mortality (neonatal mortality), alterations in growth and/or development (lower neonatal weights into post-weaning and structural abnormalities [malformations]). Functional impairment (delayed sexual maturation) was observed at 25 mg/kg/day. There was no evidence of neurobehavioral defects (maze learning and shuttle box avoidance) or immunological compromise (influenza host resistance challenge) in the F1 generation. Statistically significant decreases in the implantations and number of live fetuses were observed in the F2 generation rats of the maternal dosage group exposed to fostamatinib during pregnancy.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrTAVALISSE®
Fostamatinib Tablets
(as fostamatinib disodium hexahydrate)

Read this carefully before you start taking **TAVALISSE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TAVALISSE**.

What is TAVALISSE used for?

TAVALISSE is used to treat **adults** with a bleeding disorder known as immune thrombocytopenia (ITP) when other treatments have not worked well enough.

How does TAVALISSE work?

TAVALISSE targets an enzyme called spleen tyrosine kinase. This enzyme plays an important part in destroying platelets. Platelets are needed to stop bleeding. By limiting platelet destruction, TAVALISSE increases the number of platelets in your body.

What are the ingredients in TAVALISSE?

Medicinal ingredients: fostamatinib disodium hexahydrate

Non-medicinal ingredients: magnesium stearate; mannitol; polyethylene glycol 3350; polyvinyl alcohol; povidone; red iron oxide; sodium bicarbonate; sodium starch glycolate; talc; titanium dioxide; and yellow iron oxide.

TAVALISSE comes in the following dosage forms:

Tablets for oral administration; 100 mg, 150 mg

Do not use TAVALISSE if:

- You are allergic to
  - fostamatinib disodium hexahydrate (medicinal ingredients of TAVALISSE) or
  - any of the other ingredients in TAVALISSE
- You are pregnant or become pregnant

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TAVALISSE. Talk about any health conditions or problems you may have, including if you:

- have high blood pressure
- are pregnant or plan to become pregnant
- are breast-feeding or plan to breast-feed
- you have liver problems
- are taking any medicine that may have an effect on the way your heart beats
- have osteoporosis
- have a fracture

Other warnings you should know about:

High Blood Pressure (hypertension): New, worsening or severe high blood pressure is common in people treated with TAVALISSE. Your health care professional will check your blood pressure regularly during treatment with TAVALISSE. Your health care professional may start you on blood pressure medicine or change your current medicine to treat your blood pressure. Tell your health care professional if you get:

- headaches,
- confusion,
- dizziness,
- chest pain,
- shortness of breath.

Liver problems. Changes in liver function blood tests are common with TAVALISSE. Liver problems may occur and can be severe. Your health care professional will regularly do blood tests to check how well your liver is working during treatment with TAVALISSE. Tell your health care professional if:

- your skin and eyes appear yellowish (jaundice),
- you have abdominal pain and swelling,
- you have swelling in your legs and ankles,
- you have itchy skin,
- you have dark urine,
- you have pale stool colour,
- you have bloody or tar-coloured stool,
- you have chronic fatigue,
- you have a feeling or being sick in the stomach,
- you have a loss of appetite,
- you have an increase in liver enzymes in your blood tests.

Diarrhea. This is common and can be severe in people treated with TAVALISSE. Tell your health care professional if you get diarrhea during treatment with TAVALISSE. Your health care professional may recommend:

- changes in your diet,
- drinking more water,
- medicine to limit your symptoms.

Decrease in white blood cell counts (neutropenia). Decreases in your white blood cell count are common and can be severe with TAVALISSE. This may increase your risk of infection, including serious infections. Your health care professional will regularly do blood tests to check your white blood cell counts.

Pregnancy: You should avoid becoming pregnant while taking TAVALISSE and for at least 4 weeks after you stop taking it before planning a pregnancy.
Talk to your health care professional right away if you are pregnant or plan on becoming pregnant. TAVALISSE may cause harm to your unborn baby. Female patients must use an effective birth control method while taking TAVALISSE and for at least **4 weeks** after the last dose.

Fertility: TAVALISSE may affect the ability of a woman to get pregnant once treatment is stopped.

Breast-feeding: TAVALISSE is not recommended while breast-feeding. You should not breast-feed during treatment with TAVALISSE and for at least **4 weeks** after your last dose.

Osteoporosis or a fracture: Close monitoring of patients with osteoporosis and fractures is recommended.

Driving and Operating Machinery: Do not drive or operate machinery while taking TAVALISSE if you

- feel tired
- are dizzy
- experience any change in vision

Children (<18 years of age): TAVALISSE is not to be used in children and young adults where epiphyseal fusion (growth plate closure) has not yet occurred.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TAVALISSE:

- Ketoconazole, this medicine is typically used to treat fungal infections.
- Rifampicin (rifampin), this medicine is typically used to treat bacterial infections.
- Simvastatin and rosuvastatin, these medicines are typically used to treat high cholesterol.
- Digoxin, this medicine is typically used to treat various heart conditions such as atrial fibrillation, atrial flutter and heart failure.
- Midazolam, this medicine is typically used for sedation or to treat anxiety.
- Anticoagulants, this medicine is typically used to prevent blood clotting.
- Nelfinavir, this medicine is typically used to treat HIV infection.
- Verapamil, this medicine it typically used to treat various heart conditions such as high blood pressure.
- Ethinylestradiol, this medicine is typically used for birth control.
- Drugs that are known to strongly decrease the activity of a class of enzymes (known as CYP3A4) responsible for breaking down many drugs and toxins.

How to take TAVALISSE:
Always take this medicine exactly as your health care professional has told you. Check with your health care professional if you are not sure.

Swallow the tablets whole with water.
TAVALISSE can be taken with food or between meals.
In case of stomach upset, take the tablets with food.

Usual dose:

The recommended dose of TAVALISSE is 100 mg twice daily.
However, your health care professional will check your platelet counts during your treatment with TAVALISSE and may change your dose of TAVALISSE as needed.

After starting treatment with TAVALISSE, the dose can be increased to 150 mg twice daily based on platelet count and tolerability. A daily dose of 300 mg daily must not be exceeded.

If you have liver problems or high blood pressure, your health care professional may start you on a lower dose.

If you get serious side effects (such as high blood pressure, liver problems, diarrhea or a decrease in white blood cell counts), your health care professional may lower your dose or stop your treatment temporarily or permanently.

Overdose:

If you think you have taken too much TAVALISSE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you missed a dose of TAVALISSE, do not take a double dose to make up for a forgotten tablet. Take your next dose at its regularly scheduled time.

What are possible side effects from using TAVALISSE?

These are not all the possible side effects you may feel when taking TAVALISSE. If you experience any side effects not listed here, contact your healthcare professional.

Other side effects

- Nose Bleeds
- Shortness of breath
- Feeling sick in the stomach
- Excess gas
- Stomach pain
- Dizziness
- Tiredness (fatigue)
- Taste changes
- Rash

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
COMMON	Low white blood cell count		✓	
RARE	Severe Diarrhea	✓		
	Severe high blood pressure	✓		
	Pneumonia		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15 to 30°C). Protect from Moisture.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.

Store in the original container. Keep the bottle tightly closed.

Do not remove desiccants which are the small canisters inside the bottle which help absorb moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

If you want more information about TAVALISSE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.medison.ca, or by calling 1-800-696-1341.

This leaflet was prepared by Medison Pharma Canada Inc.

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